VERSION WITH MARKINGS TO SHOW CHANGES MADE

Amendments in the Claims

Please cancel claims 1-6 without prejudice.

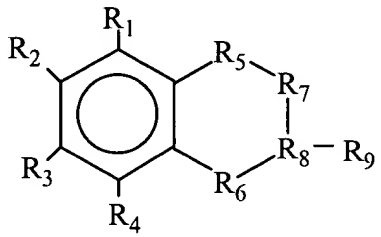
Please rewrite Claim 7 as follows:

7. (Once amended) [The angiogenesis inhibitory composition of Claim 1]An angiogenesis inhibitory composition comprising an angiogenesis inhibiting compound and an anti-inflammatory drug,

wherein the angiogenesis inhibiting compound is selected from the group consisting of:

(1) a compound selected from the formula

A)



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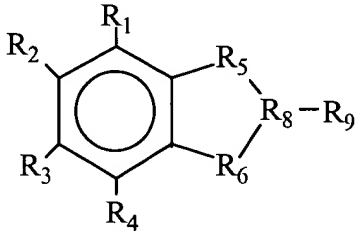
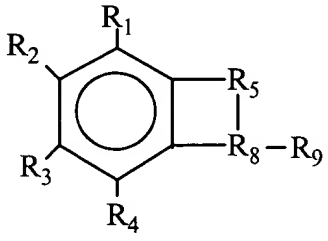


or

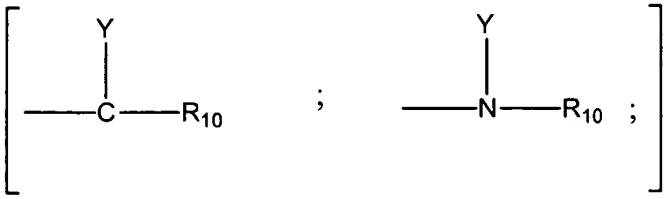
C)

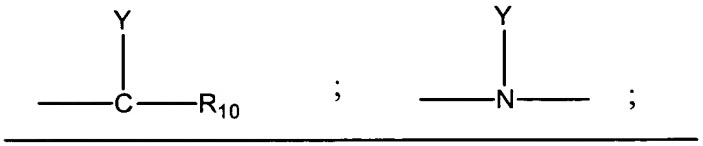


wherein

R_1 - R_4 are each independently selected from H; OH; =O; straight or branched chain alkanes, alkenes, and alkynes; cyclic alkanes, alkenes, and alkynes; combinations of cyclic and acyclic alkanes, alkenes, and alkynes; alcohol, aldehyde, ketone, carboxylic acid, ester, or ether moieties in combination with acyclic, cyclic, or combination acyclic/cyclic moieties; aza; amino; $-XO_n$ or $-O-XO_n$, where X=N and n=2, X=S and n=2 or 3, or X=P and n=1-3; and halogens;

R_5 - R_8 are each independently selected from

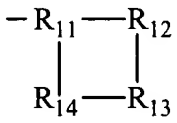




or -O-, where Y is absent and R_{10} is =O or Y and R_{10} are each independently the same as R_1;

and R_9 is a moiety selected from the group consisting of

D)



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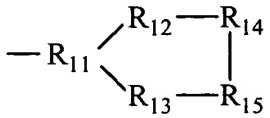

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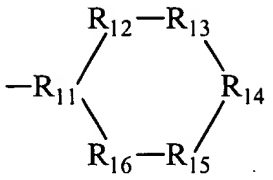
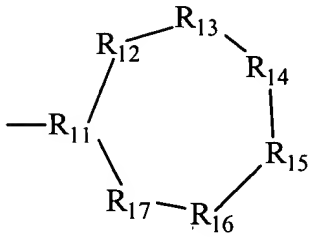
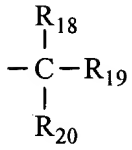


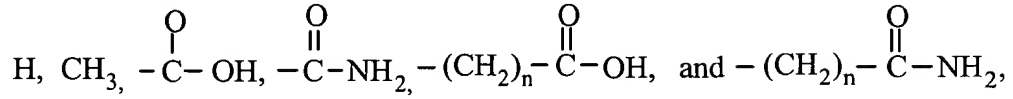
G)



and H)

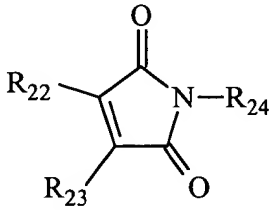


wherein each of R_{11} - R_{17} is independently the same as R_5, and wherein R_{18}, R_{19} and R_{20} are each independently selected from



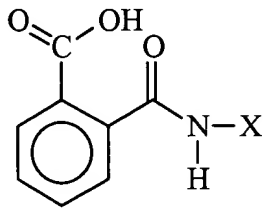
and n=1 through 4;

(2) a compound selected from the formula



where R_{22} and R_{23} are each independently H, F, Cl, Br, I, CH_3, or $-CH_2-CH_3$;
and R_{24} is H, CH_3, or $-CH_2-CH_3$;
and

(3) a compound selected from the formula



where X is R_6 as defined in (1) above.

21. (New Claim) The angiogenesis inhibitory composition of Claim 7 wherein the antiinflammatory drug is a steroid.

22. (New Claim) The angiogenesis inhibitory composition of Claim 21 wherein the steroid is selected from the group consisting of cortisol, corticosterone, hydrocortisone, hydrocortisol, cortisone, prednisone, prednisolone, dexamethasone, beclomethasone, betamethasone, mometasone, mometasone furoate, budesonide, triamcinolone acetonide, and fluticasone.

23. (New Claim) An angiogenesis inhibitory composition of Claim 7 wherein the anti-inflammatory drug is a nonsteroidal, anti-inflammatory drug (NSAID).

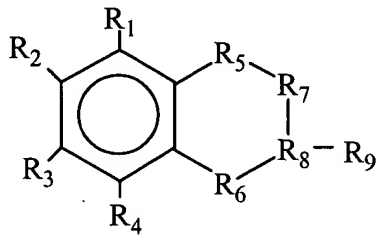
24. (New Claim) The angiogenesis inhibitory composition of Claim 23 wherein the NSAID is selected from aspirin, acetominophen, ibuprofen, esculetin, phenidone, quercetin, ketoprofen, nordihydroguiaretic acid (NDGA), sulindac, sulindac sulfone, sulindac sulfide, indomethacin, NS-398 (a cyclooxygenase-2 inhibitor), cyclooxygenase-1 inhibitors, methylheptyl imidazole, furegrelate sodium, SKF525AHCL, thromboxane inhibitors, toradol, ecasa, salsalate, diflunisal, mefenamic acid, naproxen, naproxen sodium, floctafenine, meclofenamate, phenylbutazone, oxyphenbutazone, diclofenac, etodolac, fenoprofen, flufenamic acid, flurbiprofen, pirprofen, tolmetin, apazone, fenbufen, nabumetone, oxaprozin, piroxicam, salicylate, and tenoxicam.

25. (New Claim) The angiogenesis inhibitory composition of Claim 23 wherein the NSAID is selected from indomethacin and sulindac.

26. (New Claim) A method for inhibiting angiogenesis in a human or animal comprising administering to the human or animal a composition comprising an angiogenesis inhibiting compound and an anti-inflammatory compound, wherein the angiogenesis inhibiting compound is selected from the group consisting of

(1) a compound selected from the formula

A)



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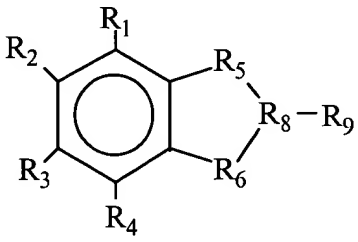
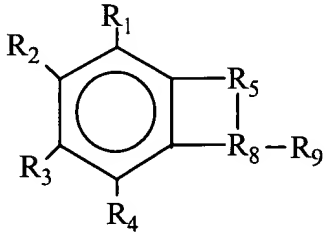


or

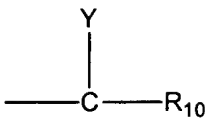
C)

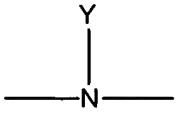


wherein

R_1 - R_4 are each independently selected from H; OH; =O; straight or branched chain alkanes, alkenes, and alkynes; cyclic alkanes, alkenes, and alkynes; combinations of cyclic and acyclic alkanes, alkenes, and alkynes; alcohol, aldehyde, ketone, carboxylic acid, ester, or ether moieties in combination with acyclic, cyclic, or combination acyclic/cyclic moieties; aza; amino; $-XO_n$ or $-O-XO_n$, where X=N and n=2, X=S and n=2 or 3, or X=P and n=1-3; and halogens;

R_5 - R_8 are each independently selected from

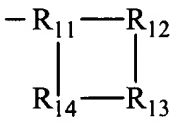


;


or -O-, where Y is absent and R_{10} is =O or Y and R_{10} are each independently the same as R_1;

and R9 is a moiety selected from the group consisting of

D)



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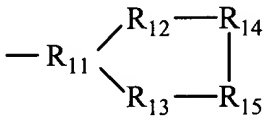

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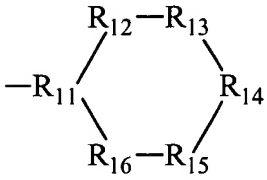

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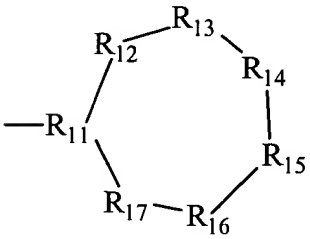
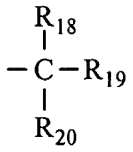
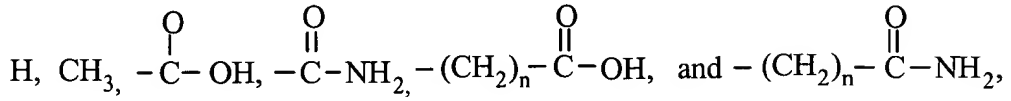


and H)

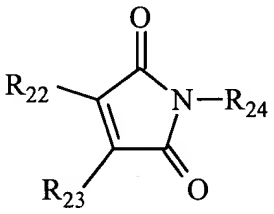


wherein each of R_{11} - R_{17} is independently the same as R_5, and wherein R_{18}, R_{19} and R_{20} are each independently selected from



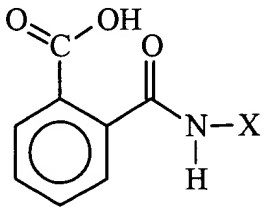
and n=1 through 4;

(2) a compound selected from the formula



where R_{22} and R_{23} are each independently H, F, Cl, Br, I, CH_3, or $-CH_2-CH_3$;
and R_{24} is H, CH_3, or $-CH_2-CH_3$;
and

(3) a compound selected from the formula



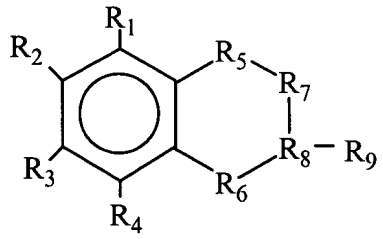
where X is R_6 as defined in (1) above; and

27. (New Claim) A method for treating an angiogenesis dependent disease in a human or animal having such a disease comprising administering to the human or animal a composition comprising an angiogenesis inhibiting compound and an antiinflammatory compound

wherein the angiogenesis inhibiting compound is selected from the group consisting of

(1) a compound selected from the formula

A)



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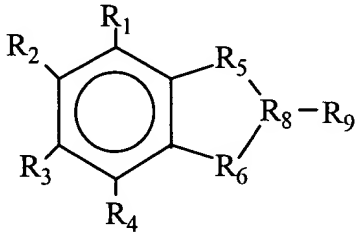
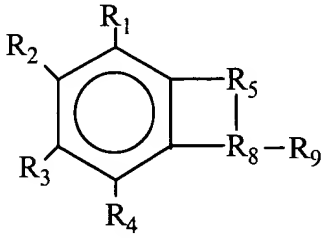


or

C)

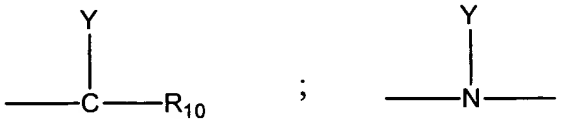


wherein

R_1 - R_4 are each independently selected from H; OH; =O; straight or branched chain alkanes, alkenes, and alkynes; cyclic alkanes, alkenes, and alkynes; combinations of cyclic and acyclic alkanes, alkenes, and alkynes; alcohol, aldehyde, ketone, carboxylic acid, ester, or ether moieties in combination with acyclic, cyclic, or

combination acyclic/cyclic moieties; aza; amino; $-XO_n$ or $-O-XO_n$, where X=N and n=2, X=S and n=2 or 3, or X=P and n=1-3; and halogens;

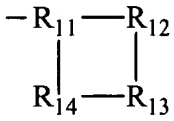
R_5 - R_8 are each independently selected from



or -O-, where Y is absent and R_{10} is =O or Y and R_{10} are each independently the same as R_1;

and R_9 is a moiety selected from the group consisting of

D)



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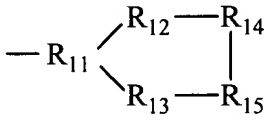

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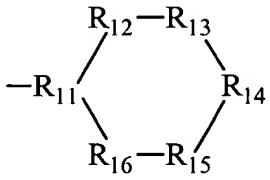
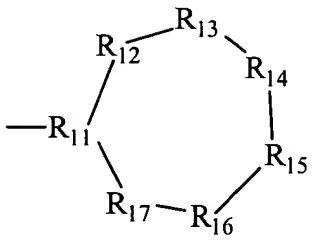
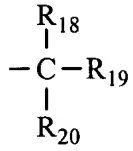


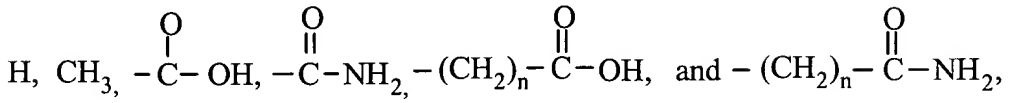
G)



and H)

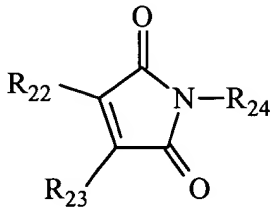


wherein each of R_{11} - R_{17} is independently the same as R_5, and wherein R_{18}, R_{19} and R_{20} are each independently selected from



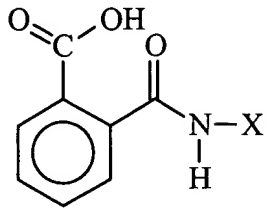
and n=1 through 4;

(2) a compound selected from the formula



where R_{22} and R_{23} are each independently H, F, Cl, Br, I, CH_3, or $-CH_2-CH_3$;
and R_{24} is H, CH_3, or $-CH_2-CH_3$;
and

(3) a compound selected from the formula



where X is R_6 as defined in (1) above.

28. (New Claim) The method of Claim 27 wherein the angiogenesis dependent disease is selected from macular degeneration, diabetic retinopathy, neovascular glaucoma, retrolental fibroplasias, proliferative vitreoretinopathy, solid tumors, blood-borne tumors, leukemia, hemangioma, psoriasis, Kaposi's sarcoma, Crohn's disease, ulcerative colitis, cancer, retinopathy of prematurity, corneal graft rejection, epidemic keratoconjunctivitis, Vitamin A deficiency, contact lens overwear, atopic keratitis, superior limbic keratitis, pterygium keratitis sicca, sjogren's syndrome, acne rosacea, phylectenulosis, syphilis, *Mycobacteria* infections, lipid degeneration, chemical burns, bacterial ulcers, fungal ulcers, *Herpes simplex* infections, *Herpes zoster* infections, Mooren's ulcer, Terrien's marginal degeneration, marginal keratolysis, trauma, rheumatoid arthritis systemic lupus, polyarteritis, Wegener's sarcoidosis, scleritis, Stevens-Johnson disease, radial keratotomy, corneal graft rejection, sickle cell anemia, pseudoxanthoma elasticum, pemphigoid, Paget's disease, vein occlusion, artery occlusion, carotid obstructive disease, chronic uveitis, chronic vitritis, Lyme's disease, systemic lupus erythematosis, Eales' disease, Behcet's disease, presumed ocular histoplasmosis, Best's disease, myopia, optic pits, Stargardt's disease, pars planitis, chronic retinal detachment, hyperviscosity syndromes, toxoplasmosis, post-laser complications, and rubeosis.

29. (New Claim) The angiogenesis inhibitory composition of Claim 7 wherein the dosage of the angiogenesis inhibiting compound is between about 0.1 to about 300 mg/kg/day.

30. (New Claim) The angiogenesis inhibitory composition of Claim 7 wherein the dosage of the angiogenesis inhibiting compound is between about 0.5 to about 50 mg/kg/day.

31. (New Claim) The angiogenesis inhibitory composition of Claim 7 wherein the dosage of the angiogenesis inhibiting compound is between about 1 to about 10 mg/kg/day.

32. (New Claim) The method of Claim 26 wherein the composition comprises a formulation suitable for oral, rectal, ophthalmic, nasal, topical, vaginal, or parenteral administration.

33. (New Claim) The method of Claim 22 wherein the composition comprises a formulation suitable for oral, rectal, ophthalmic, nasal, topical, vaginal, or parenteral administration.

34. (New Claim) The method of Claim 26 wherein the dosage of the angiogenesis inhibiting compound is between about 0.1 mg/kg/day to about 300 mg/kg/day.

35. (New Claim) The method of Claim 26 wherein the dosage of the angiogenesis inhibiting compound is between about 0.5 mg/kg/day to about 50 mg/kg/day.

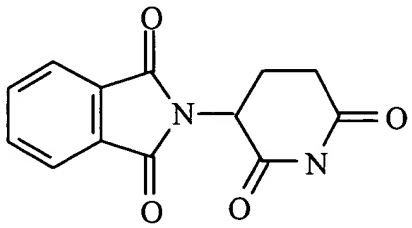
36. (New Claim) The method of Claim 26 wherein the dosage of the angiogenesis inhibiting compound is between about 1 mg/kg/day to about 10 mg/kg/day.

37. (New Claim) The method of Claim 27 wherein the dosage of the angiogenesis inhibiting compound is between about 0.1 mg/kg/day to about 300 mg/kg/day.

38. (New Claim) The method of Claim 27 wherein the dosage of the angiogenesis inhibiting compound is between about 0.5 mg/kg/day to about 50 mg/kg/day.

39. (New Claim) The method of Claim 27 wherein the dosage of the angiogenesis inhibiting compound is between about 1 mg/kg/day to about 10 mg/kg/day.

40. (New Claim) An angiogenesis inhibitory composition comprising an angiogenesis inhibiting compound and an anti-inflammatory drug,
wherein the angiogenesis inhibiting compound has the formula



41. (New Claim) The angiogenesis inhibitory composition of Claim 40 wherein the antiinflammatory drug is a steroid.

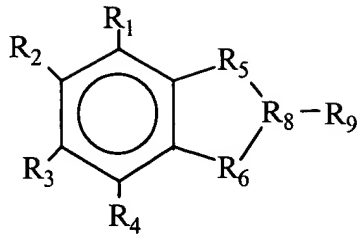
42. (New Claim) The angiogenesis inhibitory composition of Claim 41 wherein the steroid is selected from the group consisting of cortisol, corticosterone, hydrocortisone, hydrocortisol, cortisone, prednisone, prednisolone, dexamethasone, beclomethasone, betamethasone, mometasone, mometasone furoate, budesonide, triamcinolone acetonide, and fluticasone.

43. (New Claim) An angiogenesis inhibitory composition of Claim 11 wherein the anti-inflammatory drug is a nonsteroidal, anti-inflammatory drug (NSAID).

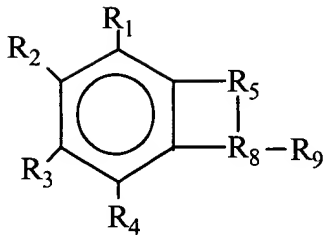
44. (New Claim) The angiogenesis inhibitory composition of Claim 43 wherein the NSAID is selected from aspirin, acetominophen, ibuprofen, esculetin, phenidone, quercetin, ketoprofen, nordihydroguiaretic acid (NDGA), sulindac, sulindac sulfone, sulindac sulfide, indomethacin, NS-398 (a cyclooxygenase-2 inhibitor), cyclooxygenase-1 inhibitors, methylheptyl imidazole, furegrelate sodium, SKF525AHCL, thromboxane inhibitors, toradol, ecasa, salsalate, diflunisal, mefenamic acid, naproxen, naproxen sodium, floctafenine, meclofenamate, phenylbutazone, oxyphenbutazone, diclofenac, etodolac, fenoprofen, flufenamic acid, flurbiprofen, pirprofen, tolmetin, apazone, fenbufen, nabumetone, oxaprozin, piroxicam, salicylate, and tenoxicam.

For specification (page 14):

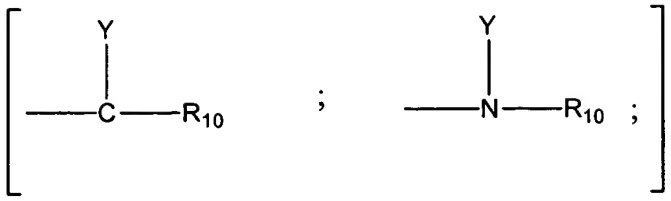
B)

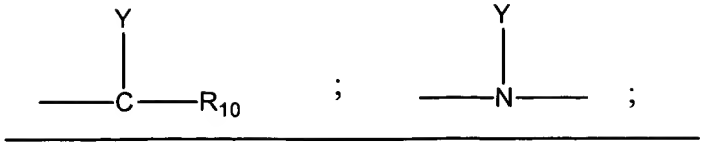


C)



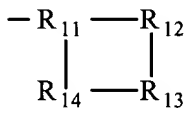
In the above formulae, A), B), and C), R_1, R_2, R_3 and R_4 can be selected from: -H; -OH; =0, straight and branched chain alkanes, alkenes, alkynes; cyclic alkanes, alkenes, and alkynes; combinations of cyclic and acyclic alkanes, alkenes, and alkynes; alcohol, aldehyde, ketone, carboxylic acids, esters, or ether moieties in combination with acyclic, cyclic, or combination acyclic/cyclic moieties; aza; amino; $-XO_n$ or $-O-XO_n$, where X=N and n=2; X=S and n=2 or 3; or X=P and n=1-3; or X=P and n=1-3; and halogens; R_5, R_6, R_7, and R_8 are each independently selected from:



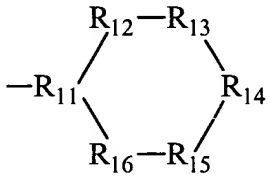


or –O- where Y is optional and is the same as defined above for $R_{1;}$ and R_{10} is the same as defined above for R_1 and R_{10} is the same as defined above for $R_{1,}$ or when Y is absent, R_{10} is =0; and R_9 is a moiety having formula D), E), F), G), or H):

D)



F)



REMARKS

Claims 1-12 are pending in the present application. By this amendment, Claims 1-6 are cancelled, Claim 7 has been amended, and Claims 21-44 have been added. New Claims 21-44 find support in the specification including page 23 lines 23-25, and in original claims 1-6, and original claims 13-20.

The scope of Claim 7 has not been changed by this amendment as Claim 7 has been rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Applicants respectfully request reconsideration of the present claims in view of the foregoing amendments and the following remarks.

I. Formal Matters:

Applicant has elected with traverse Group I Claims 1-12 responsive to the Election Restriction requirement of September 13, 2000. Claims 13-20 have been withdrawn by the Examiner. Applicant reserves the right to file divisional applications for any withdrawn claims.

II. Prior Art Rejections:

A. Rejection of Claims 1 and 3 Under 35 U.S.C. § 102(b)

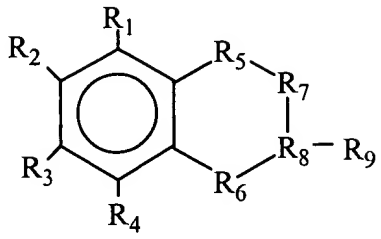
Claims 1 and 3 were rejected under 35 U.S.C. §102(b) as being anticipated by the abstract for "Pentosan inhibits angiogenesis in vitro and suppresses prostate tumor growth in vivo", by Nguyen et al, Anticancer Research 1993, pp 2143-7 (hereafter "Nguyen"). Claims 1-6 are cancelled which renders the rejection moot.

Should the Examiner maintain the rejection as to Claim 7, Applicant respectfully submits that Nguyen does not teach or suggest Applicant's invention as claimed. Claim 7 is directed to an angiogenesis inhibitory composition comprising an angiogenesis inhibiting compound and an anti-inflammatory drug,

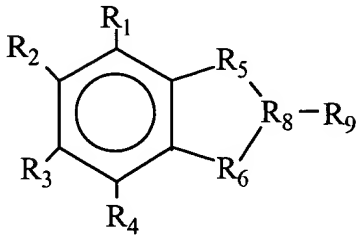
wherein the angiogenesis inhibiting compound is selected from the group consisting of:

(1) a compound selected from the formula

A)

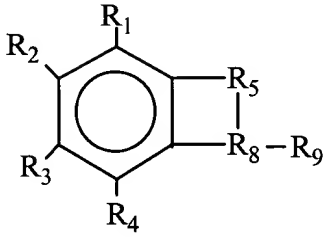


B)



or

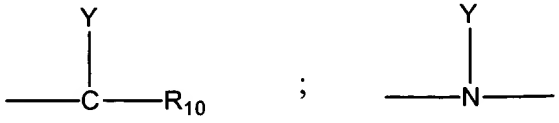
C)



wherein

R_1 - R_4 are each independently selected from H; OH; =O; straight or branched chain alkanes, alkenes, and alkynes; cyclic alkanes, alkenes, and alkynes; combinations of cyclic and acyclic alkanes, alkenes, and alkynes; alcohol, aldehyde, ketone, carboxylic acid, ester, or ether moieties in combination with acyclic, cyclic, or combination acyclic/cyclic moieties; aza; amino; $-XO_n$ or $-O-XO_n$, where X=N and n=2, X=S and n=2 or 3, or X=P and n=1-3; and halogens;

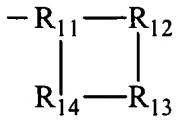
R_5 - R_8 are each independently selected from



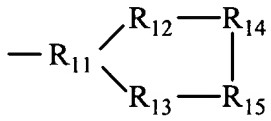
or -O-, where Y is absent and R_{10} is =O or Y and R_{10} are each independently the same as R_1;

and R_9 is a moiety selected from the group consisting of

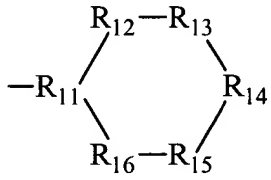
D)



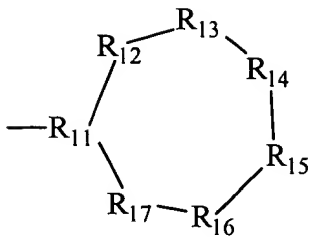
E)



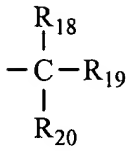
F)



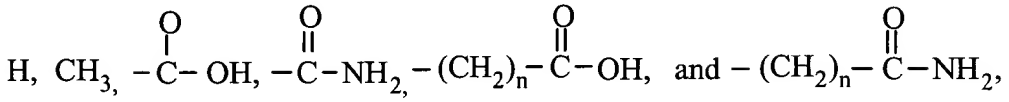
G)



and H)

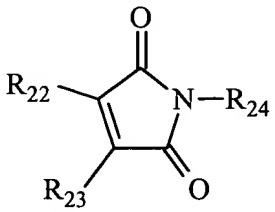


wherein each of R_{11} - R_{17} is independently the same as R_5, and wherein R_{18}, R_{19} and R_{20} are each independently selected from



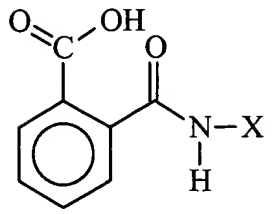
and n=1 through 4;

(2) a compound selected from the formula



where R_{22} and R_{23} are each independently H, F, Cl, Br, I, CH_3, or $-CH_2-CH_3$;
and R_{24} is H, CH_3, or $-CH_2-CH_3$;
and

(3) a compound selected from the formula



where X is R_6 as defined in (1) above.

Nguyen teaches that pentosan, in combination with hydrocortisone, inhibits endothelial cell motility and tubule formation in vitro and inhibits capillary formation in the chicken chorioallantoic membrane assay. Nguyen does not teach or suggest any compound that falls within the scope of the generic structure as defined by Claim 7.

For a reference to qualify as prior art under 35 U.S.C. § 102(b), it is well established that the reference alone must teach each and every element of the claimed invention. See *Hybritech Inc. v. Monoclonal Antibodies, Inc.,* 802 F.2d 1367, 1379, 213 U.S.P.Q. 81 90 (Fed. Cir. 1986). Missing elements may not be supplied by the knowledge of one skilled in the art or the disclosure of another reference. See *Structural Rubber Prods. Co. v. Park Rubber Co.,* 749 F.2d 707m 716, 223 U.S.P.Q. 1264, 1271 (Fed. Cir. 1984).

It is respectfully submitted that Nguyen fails to anticipate Applicant's claimed invention because Nguyen does not teach or suggest the generic structure as defined by Claim 7 and therefore does not teach each and every element of the claimed invention. Therefore, for at least the reasons given above, Applicant respectfully submits that Claim 7 is not anticipated and is allowable over the art of record. Furthermore, since claims 8-12 and claims 21-25 recite additional claim features and depend from claim 7, these claims are also allowable over the art of record. Accordingly, Applicant respectfully requests withdrawal of this rejection.

B. Rejection of Claims 1 and 5-20 Under 35 U.S.C. § 102(b)

Claims 1 and 5-20 were rejected under 35 U.S.C. §102(b) as being anticipated by WO 94/23725, issued to Willoughby (hereafter "Willoughby"). This rejection is respectfully traversed. Claims 1-6 are cancelled and render the rejection of claims 1 and 5-6 moot. Furthermore, Applicant is confused by the rejection of claims 5-20 because claims 13-20 were not elected for examination. Therefore, Applicant will respond to the rejection of claims 1 and 5-12.

As to Claim 7, Applicant respectfully submits that Willoughby fails to teach or suggest Applicant's invention as claimed. Claim 7 is directed to the invention as stated above.

Willoughby teaches administering a composition of NSAID and hyaluronic acid for inhibition, control and regression of angiogenesis (page 7 lines 12-23). Willoughby does not teach or suggest any compound that falls within the scope of the generic structure as defined by Claim 7.

It is respectfully submitted that Willoughby fails to anticipate Applicants' claimed invention because it does not teach or suggest the generic structure as defined in Claim 7 and therefore does not teach each and every element of Applicants' invention as claimed.

Therefore, for at least the reasons given above, Applicant respectfully submits that Claim 7 is not anticipated and is allowable over the art of record. Furthermore, since claims 8-12 and claims 21-25 recite additional claim features and depend from claim 7, these claims are also allowable over the art of record. Accordingly, Applicants respectfully request withdrawal of this rejection.

C. Rejection of Claims 1-12 Under 35 U.S.C. § 103(a)

Claims 1-12 are rejected under 35 USC 103(a) as being unpatentable over Willoughby et al WO 94/23725 in view of Colville-Nash et al. Claims 1-6 are cancelled which renders this rejection moot as to those claims.

As to claim 7, Applicant respectfully submits that Willoughby in view of Colville-Nash fails to teach or suggest Applicant's invention as claimed. Willoughby fails to teach or suggest any compound that falls within the scope of generic structures

defined by Claim 7, as explained supra. Furthermore, the teachings of Colville-Nash do not teach or suggest such a compound. The prior art reference or combination of references must teach or suggest all the limitations of the claims (In re Wilson, 165 U.S.P.Q. 494, 496 (C.C. P.A. 1970).

The combination of Willoughby and Colville-Nash fails to teach or suggest Applicant's invention because the combination does not provide a compound that falls within the scope of generic structures as defined by Claim 7.

For at least the reasons given above, Applicants respectfully submit that the teachings of Willoughby and Collville-Nash, either taken alone or in combination fail to teach or suggest Applicants' claimed invention. Furthermore, since claims 8-12 and claims 21-25 recite additional claim features and depend from claim 7, these claims are also allowable over the art of record. Accordingly, withdrawal of this rejection is respectfully requested.

It is noted that the application has been searched to the extent of the elected species, however, as the present claims are not anticipated or obvious over the prior art of record, Applicant understands that the search will be extended to the extent necessitated to determine patentability of the generic claims.

D. Rejoinder of Method Claims

Process claims which depend from or otherwise include all the limitations of the patentable product will be entered as a matter of right if the amendment is presented prior to final rejection or allowance (MPEP 821.04 second paragraph). Applicant has submitted process claims 26-28 and 32-39 and requests rejoinder and examination as a matter of right upon allowance of the composition claims. Applicant respectfully requests allowance because these claims contain all the limitations and have the same scope as the product claim 7 which Applicant submits is allowable for the reasons stated supra.

III. Conclusion

Applicants respectfully submit that Claims 7-12 and 21-44 define patentable subject matter. Accordingly, the Applicants respectfully request allowance of these claims.

Should the Examiner believe that anything further is necessary to place the application in better condition for allowance, the Examiner is respectfully requested to contact Applicants' representative at the telephone number listed below.

A check in the amount of $362.00 is enclosed to cover the additional claims. The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No.11-0855.

Respectfully submitted,

Cheryl S. Huseman

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